AR 201-12966B3

IRGAFOS 168

Tris(2,4-di-(tert)-butylphenyl)phosphite

CAS No. 31570-04-4

Name of Sponsoring Organization:	Ciba Specialty Chemicals Corporation
HPV Registration Number:	
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CONTENTS

SUMMARY TABLE

CAS No. 31570-04-4 PHYSICAL/CHEMICAL ELEMENTS	DATE	RESULTS	FULFILLS REQUIREMENT
Melting Point	2000	181 - 184 °C	Yes
Boiling Point	2000	619.8 °C	Yes
Vapor Pressure	2000	4.9×10^{-13} mm Hg (25 °C)	Yes
Partition Coefficient	2000	log P = 18.1	Yes
Water Solubility	1992	$< 9 \times 10^{-5}$ g/L (20 °C)	Yes
ENVIRONMENTAL FATE ELEMENTS			
Photodegradation	2000	For reaction with hydroxyl radical, predicted rate constant = 23.9×10^{-12} cm^3/molecule-sec predicted half-life = 5.4 h	Yes
Stability in Water	2001	Unable to determine	Yes
Fugacity	2000	Predicted distribution using Level III Fugacity Model Air 5.1×10^{-5} % Water 5.6×10^{-3} % Soil 99.3 % Sediment 0.65 % Persistence = 3.9×10^{6} h	Yes
Biodegradation	1989	Not biodegradable 3 - 6% after 28 days	Yes
ECOTOXICITY ELEMENTS			
Acute Toxicity to Fish	1976	LC_{50} Bluegill (Lepomis macrochirus): 84 ppm Rainbow trout (Salmo gairdneri): 49 ppm Carp (Cyprinus carpio): 66 ppm Catfish (Ictalurus melas): 70 ppm Golden orfe (Leucuscus idus forma orfus): 42 ppm	Yes
Toxicity to Aquatic Plants	1993	Green algae (Scenedesmus subspicatus): EC_{50}, growth (O-72 h) > 75.2 mg/L NOEC, growth (O-72 h) = 75.2 mg/L	Yes
Acute Toxicity to Aquatic Invertebrates	1988	Daphnia magna: EC_{50} (24 h) calculated = 5 10 mg/L EC_0 (24 h) = 180 mg/L EC_{100} (24 h) = 1000 mg/L	Yes

SUMMARY TABLE, CONTINUED

CAS No. 31570-04-4 HEALTH ELEMENTS	DATE	RESULTS	FULFILLS REQUIREMENT
Acute Toxicity	1974	Rat: LD_{50} (Oral) > 6000 mg/kg	Yes
	1992	Rat: LD_{50} (Dermal) > 2000 mg/kg	Yes
Genetic Toxicity in vivo	1982, 1989	Chinese hamster: No evidence of effect on sister chromatid exchange	Yes
	1982	Mouse: No evidence of chromosomal aberrations	
	1982	Chinese hamster: No evidence of effect on chromatid or chromosome-type aberrations	Yes
	1980	Chinese hamster: No evidence of increase in bone marrow cells with anomalies of nuclei	Yes
	1978	Mouse: No evidence of dominant lethal effects or reduced fertility	Yes
Genetic Toxicity in vitro	1978	Salmonella typhimurium: Not mutagenic	Yes
	1982	Saccharomyces cerevisiae: Not mutagenic	Yes
Repeated Dose Toxicity	1975	Rat: NOEL = 250 mg/kg/day	Yes
	1976	Rat: NOEL = 500 mg/kg/day	Yes
	1978	Dog: NOEL > 318 mg/kg/day	Yes
Reproductive Toxicity	1985	Rat: No evidence of reproductive toxicity	Yes
Developmental Toxicity/ Teratogenicity	1983	Rabbit: Not teratogenic	Yes

1. MELTING POINT

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4
Method:	From Aldrich. [1]
GLP:	No
Year:	2ooo
Results:	181 - 184°C
Remarks:	A similar melting point (181 ▪ 186 °C) was reported by Ciba Specialty Chemicals Corp. The method of determination by Aldrich or Ciba was not reported. The melting point was assigned a reliability code of 2g (data from handbook or collection of data).*
References:	'Sigma-Aldrich.com [2]See general reference, p. 53.

2. BOILING POINT

Test substance:	**Tris(2,4-di-(tert)-butylphenyl)phosphite** CAS No. 3 1570-04-4
Method:	Estimated by the MPBPWIN Program (v. 1.40) using the adapted Stein and Brown method. [1,2]
GLP:	No
Year:	2000
Results:	619.8 °C
Remarks:	In the absence of reliable experimental data, the boiling point was calculated using an accepted method and assigned a reliability code of 2f (accepted calculation method).[3]
References:	'Syracuse Research Corporation, Syracuse, NY *Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [3]See general reference, p. 53

3. VAPOR PRESSURE

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Estimated by the MPBPWIN Program (v. 1.40) using the modified Grain method.[1,2]
GLP:	No
Year:	2000
Results:	4.9 x 10^{-13} mm Hg, 25 °C
Remarks:	The MSDS from Ciba Specialty Chemicals Corp reported a vapor pressure of 1 x 10^{-10} mm Hg at 20 °C, but the method of determination was not reported. In the absence of this information, the vapor pressure was calculated using an accepted method and assigned a reliability code of 2f (accepted calculation method).[3]
References:	'Syracuse Research Corporation, Syracuse, NY [2]Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [3]See general reference, p. 53.

4. PARTITION COEFFICIENT

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4
Method:	Estimated by the KOWWIN Program (v. 1.66).[1,2]
GLP:	No
Results:	Log P = 18.1
Remarks:	The MSDS from Ciba Specialty Chemicals Corp reported a partition coefficient of >> 6, but the method of determination was not reported. In the absence of this information, the partition coefficient was calculated using an accepted method and assigned a reliability code of 2f (accepted calculation method).[3]
References:	Syracuse Research Corporation, Syracuse, NY *Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [3]See general reference, p. 53

5. WATER SOLUBILITY

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4
Method:	EEC Directive 84/449 A.6; OECD Guideline 105 The flask method was applied instead of the column, as a change in crystal structure might occur when the test substance was deposited on the support material.
GLP:	No
Results:	Water solubility was below the detection limit. $< 9 \times 10^{-5}$ g/L (20 °C)
Remarks:	This study was assigned a reliability code of 2a, as it was conducted under EEC and OECD, but not GLP guidelines.*
References:	"'Water solubility, TK 11682," Ciba Geigy Ltd., Basel, Switzerland, 2/26/92. [2]See general reference, p. 53

6. PHOTODEGRADATION

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4
Method:	Estimated by the AOP program which estimates rate constants and half-lives of atmospheric reactions of organic compounds with hydroxyl radicals and ozone in the atmosphere.[1,2]
GLP:	No
Results:	For reaction with hydroxyl radicals, the half-life of the chemical was predicted to be moderate. Rate constant: 23.9 x 10^{-12} cm^3/molecule-sec Half-life: 5.4 h
Remarks:	In the absence of reliable experimental data, the photodegradation was calculated using an accepted method and assigned a reliability code of 2f (accepted calculation method).'
References:	'Syracuse Research Corporation, Syracuse, NY [2]Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [3]See general reference, p. 53

7. STABILITY IN WATER

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4
Method:	OECD Guideline 111
GLP:	No
Year:	2001
Results:	Due to its low water solubility, we were unable to experimentally determine hydrolysis.[1] The HYDROWIN Program (v. 1.67)[2,3] also was unable to evaluate this chemical structure.
References:	"'Hydrolysis of Irgafos 168 as a function of pH," Expert statement by Michael Ruberto, Ciba Specialty Chemicals Corp., Tarrytown, NY, 3/2/2001. *Syracuse Research Corporation, Syracuse, NY [3]Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

8. THEORETICAL DISTRIBUTION (F'UGACITY CALCULATION)

Test substance:	**Tris(2,4-di-(tert)-butylphenyl)phosphite** CAS No. 3 1570-04-4
Method:	Estimated by EQC Level III Fugacity Model.'
Year:	2000
GLP:	No
Results:	Distribution using Level III Fugacity Model

Air	5.1 x 10^{-5} %
Water	5.6 x 10^{-3} %
Soil	99.3 %
Sediment	0.65 %

Persistence = 3.9 x 10^{6} h

Remarks: In the absence of reliable experimental data, the fugacity was calculated using an acceptable method and assigned a reliability code of 2f (accepted calculation **method).**[3]

References: 'Environmental Modelling Centre, Trent University, Peterborough, Ontario, 1997

[2]**See** general reference, p. 53

9. BIODEGRADATION

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4 Batch No. EN 128985.82
Method:	OECD Guideline No. 301B (Paris 1981). Bacteria was collected from activated sludge of a sewage treatment plant. The preparation was carried out according to the method described in the guideline. The volume of the test solution was reduced from 3 L to 1.5 L. Due to the poor solubility of the test substance in water, an emulsifier was used to achieve a better distribution in the medium. The test substance was added to the medium and homogenized with Nonylphenol 10EO5PO. The CO_2 formed by biodegradation was absorbed with NaOH and determined on a carbon analyzer.
Test Type:	Aerobic
Inoculum:	Fresh sewage treatment plant sample (per guideline).
Medium:	Sewage sludge (per guideline)
Concentration of the chemical:	11.4 mg/L 21.5 mg/L
GLP:	No
Year:	1989
Results:	11.4 mg test substance/l = 6% in 28 days 21.5 mg test substance.& = 3% in 28 days
Conclusion:	This chemical was not biodegradable in this test.
Remarks:	This study is assigned a reliability code of 2a, as it was conducted under OECD, but not GLP guidelines.*
Reference:	'Report on the test for ready biodegradability of TK 11682 in the modified Sturm test. Project No. 88 45 80, Ciba-Geigy Ltd., Base1 Switzerland, 1989. [2]See general reference, p. 53.

10. ACUTE TOXICITY TO FISH

Test substance: **Tris(2,4-di-(tert)-butylphenyl)phosphite**
CAS No. **31570-04-4**

Method: Test was based on the method reported by Bathe *et al.*[2] Fish were placed in 12 L tanks containing reconstituted water, which was prepared by dissolving 30 mg $CaSO_4$, 30 mg $MgSO_4$, 48 mg $NaHCO_3$, and 3 mg KC1 per liter deionized water. The test material was dissolved in acetone and added to the tanks. Although the amount of acetone used was not provided in the report, volumes were the same in all dose groups and controls. The tanks were maintained at 14 ± 2 °C (trout, carp, bluegill) or 22 ± 2 °C (catfish, golden orfe). With the exception of experiments on trout, the water was not aerated during testing. Dissolved oxygen and pH were monitored at 24 h intervals throughout the 96 h testing period. Four fish were placed per tank.

Species: Bluegill (Lepomis macrochirus), 56 mm mean length, 3.4 g mean weight
Rainbow trout (Salmo gairdneri), 55 mm, 1.3 g
Carp (Cyprinus carpio), 59 mm, 3.4 g
Catfish (Ictalurus melas), 62 mm, 2.4 g
Golden orfe (Leuciscus idus forma orfus, 62 mm, 1.9 g

Exposure period: 96 h

GLP: No

Year: 1976

Results:

Species	LC50 (96 h)
Bluegill (Lepomis macrochirus)	84 ppm (nominal)
Rainbow trout (Salmo gairdneri)	49 ppm (nominal)
Carp (Cyprinus carpio)	66 ppm (nominal)
Catfish (Ictalurus melas)	70 ppm (nominal)
Golden orfe (Leuciscus idus forma orfus	42 ppm (nominal)

Table 1. Oxygen content data (mg

Time, h	DI water	Rainbow trout*	Carp	Catfish	Bluegill	Golden orfe
0	12.6		10.0	10.8	10.0	11.2
24	12.6		7.5	6.7	6.3	7.2
48	12.6		6.6	6.0	4.8	4.4
72	12.6		6.1	5.5	4.2	4.1
96	12.6		5.5	5.0	3.8	3.8

*Continuous aeration throughout treatment; oxygen content was not determined.

Table 2. pH data

Time, h	DI water	Rainbow trout	Carp	Catfish	Bluegill	Golden orfe
0	7.6	7.6	7.6	7.6	7.6	7.6
24	7.6	7.1	7.1	7.0	7.0	7.3
48	7.6	7.2	7.1	7.3	7.1	7.3
72	7.6	7.2	7.0	7.2	7.1	7.2
96	7.6	7.2	7.0	7.2	7.1	7.2

Table 3. Mortality data for bluegill

Concentration ppm	No. fish tested	24 h	48 h	72 h	96 h	% Mortality, 96 h
Vehicle control	12	0	0	0	0	0
65	12	0	0	0	0	0
87	12	0	1	7	8	66.7
100	12	0	2	10	11	91.7

Table 4. Mortality data for rainbow trout

Concentration ppm	No. fish tested	24 h	48 h	72 h	96 h	% Mortality, 96 h
Vehicle control	12	0	0	0	0	0
37	12	0	0	0	0	0
49	12	0	0	5	6	50
65	12	0	4	12	12	100

Table 5. Mortality data for carp

Concentration ppm	No. fish tested	24 h	48 h	72 h	96 h	% Mortality, 96 h
Vehicle control	12	0	0	0	0	0
28	12	0	0	0	0	0
49	12	0	0	0	2	16.7
65	12	0	1	1	4	33.3
87	12	0	8	10	11	91.7

Table 6. Mortality data for catfish

Concentration ppm	No. fish tested	24 h	48 h	72 h	96 h	% Mortality, 96 h
Vehicle control	12	0	0	0	0	0
37	12	0	0	0	1	8.3
65	12	0	1	2	3	25
87	12	3	10	12	12	100

Table 7. Mortality data for golden orfe

Concentration ppm	No. fish tested	24 h	48 h	72 h	96 h	% Mortality, 96 h
Vehicle control	12	0	0	0	0	0
37	12	0	1	1	1	8.3
49	12	0	3	12	12	100
65	12	5	12	12	12	100

Remarks: This study was not conducted under OECD or GLP guidelines. The study was assigned a reliability code of 2e (meets generally accepted scientific standards, is well documented, and is acceptable for assessment).[3]

References: "'Acute toxicity to rainbow trout, carp, catfish, bluegill and golden orfe of TK 11682." Siss 5496, Ciba-Geigy Ltd, Basel, Switzerland, 1976.

[2]Bathe, R., Sachsse, K., Ullmann, L., Hormann, W.D., Zak, F., and Hess, R., "The evaluation of fish toxicity in the laboratory." In Proceedings of the European Society of Toxicology, Vol XVI, pp. 113-124, 1974.

[3]See general reference, p. 53.

11. TOXICITY TO AQUATIC PLANTS

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4 Batch No. N 26824 Purity > 99%
Method:	87/302/EEC page 89-94 Algal growth inhibition test. Determination of EbC 50: concentration which reduced the growth of algae 50% relative to control. Studies were performed using 100 mL Erlenmeyer flasks, containing 50 mL test solution and stoppered with aluminum caps. Temperature was 23 ± 2 °C; pH ranged from 7.8 to 7.9 at 0 h and from 8.8 to 10.0 at 72 h. No information was provided on dissolved oxygen or water hardness. Nominal test concentrations were 1.23, 3.7, 11, 33, and 100 mg/L. Polyoxy-ethylene-sorbitan-monooleate (TWEEN80) (3.6 mg/L) was added to enhance solubility. Samples for analysis were taken at 0 and 72 h. Each test concentration was tested in 3 replicates and the blank control in 6 replicates. Continuous illumination was provided by cold white fluorescent light (120 Initial cell density was 11000 cell/mL. Cell densities were measured at 24, 28, and 72 h.
Species:	Green Algae (Scenedesmus subspicatus)
Test concentrations (measured):	1.1, 3.1, 8.1, 23.8, 75.2 mg/L
Exposure period:	72 h
Analytical monitoring:	Yes
GLP:	Yes
Year:	1993
Results:	EbC_{50} (O-72 h) > 75.2 mg/L (measured concentration) NOEbC (O-72 h) = 75.2 mg/L (measured concentration)

Table 1. Analytical data of test concentrations

Nominal Concentration, mg/L	Measured concentration 0h	72 h
Vehicle	< 0.2	< 0.2
1.23	1.4	1.1
3.7	3.8	3.1
11	11.1	8.1
33	32.3	23.8
100	96.1	75.2

Remarks: This study was assigned a reliability code of 1 (reliable without restrictions) according to the criteria established by Klimisch *et al* (1997).[2]

Reference: "'Report on the growth inhibition test of IRGAPOS 168 to Green Algae (Scenedesmus subspicatus)." Test No. 928 138, Ciba-Geigy Limited, Basel, Switzerland, 1993.

[2]See general reference, p. 53.

12. ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4 Batch No. EN 128985.82
Method:	OECD Guideline No. 202, Part I, 1984. Determination of EC50 (24 h), the concentration at which 50% of the population is immobilized. Tests were performed using beakers containing 100 mL test solution. Reconstituted water was prepared by dissolving 65 mg $NaHCO_3$, 294 mg $CaCl_2$ (2 H_2O), 123 mg $MgSO_4$ (7 H_2O), and 6 mg KC1 in 1 L bidistilled water. Total hardness was 240 mg $CaCO_3$/L; temperature was 20 ± 1 "C; pH ranged from 7.5 to 7.8; O_2 ranged from 95 to 99% saturation. A stock solution was prepared by mixing 2 g test material and 8 mg alkylphenol-polyglykol-ether in 2000 mL water. Test concentrations (nominal) were 32, 58, 100, 180, 320, 580, and 1000 mg/L. Initially, the test substance appeared homogeneously distributed in the test vessels. A slight deposit was observed at concentrations 32 to 1000 mg/L after 24 h exposure. Vehicle control contained alkylphenol-polyglykol-ether at a concentration of 4 mg/L. There were 20 daphnia per concentration and control (4 replicates of 5 daphnia each).
Type of test:	Static
Species:	Daphnia magna Straus 1820
No. animals:	20 daphnia/concentration and control (4 replicates of 5 daphnia each)
Exposure period:	24 h
Analytical monitoring:	No
GLP:	No
Year:	1988
Results:	EC_{50} (24 h) calculated = 5 10 mg/L (nominal) EC_0 (24 h) = 180 mg/L (nominal) EC_{100} (24 h) = 1000 mg/L (nominal)

Table 1. Summary data of immobilization after 24 h exposure

Concentration, nominal mg/L	Total number	Total percent
Blank	0/20	0
Vehicle	0/20	0
32	0/20	0
58	0/20	0
loo	0/20	0
180	0/20	0
320	1/20	5
580	13/20	65
1000	20/20	100

Remarks: This study was assigned a reliability code of **2a,** as it was conducted under OECD, but not GLP guidelines.*

Reference: '"Test for acute toxicity of TK 11682 to Daphnia magna." Project No. 884581. Ciba-Geigy Limited, Basel, Switzerland, 1988.

[2]See general reference, p. 53.

13. ACUTE TOXICITY

A. ORAL

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4
Method:	Rats, 6 to 7 weeks old and weighing 160 to 180 g, were used in this study. The test substance was suspended in polyethylene glycol (PEG 400) and administered to rats by gavage. Following single exposure, animals were observed for up to 7 additional days.
Species/strain:	Rat [Tif:RAI]
Sex:	20 Male; 20 Female
No. Animals/Group:	5 Male and 5 female rats/group
Doses:	1000, 3170, 4640, 6000 mg/kg
Vehicle:	PEG 400
Post dosing observation period:	7 days
GLP:	No
Year:	1974
Results:	LD_{50} > 6000 mg/kg[1] Within 2 h after exposure, the rats exhibited sedation, dyspnoea, exophthalmus, curved position, and ruffled fur. Animals recovered within 6 to 7 days. No deaths occurred during the study. No gross abnormalities were observed at necropsy.
Remarks:	Rats were observed for 7 days post-exposure, rather than the recommended 14-days. However, the results were consistent with two other studies that reported an acute oral LD_{50} > 6000 mg/kg in the mouse,* and > 6000 mg/kg in the Chinese hamster.[3] In these studies, animals were observed for 14-days post-exposure. This study was not conducted under OECD or GLP guidelines. The study was assigned a reliability code of 2e (meets generally accepted scientific standards, is well documented, and is acceptable for assessment).[4]
References:	"'Acute oral LD50 of TK-11682 in the rat." Project No. Siss 3863, Ciba-Geigy Limited, Basel, Switzerland, 1974.

[2]"Acute oral LD50 in the mouse of TK 11682." Project No. Siss 6236, Ciba-Geigy Limited, Basel, Switzerland, 1977a.

"Acute oral LD50 in the Chinese hamster [Cricetulus griseus] of TK 11682." Siss 6236, Ciba-Geigy Limited, Basel, Switzerland, 1977b.

[4]See general reference, p. 53.

B. DERMAL

Test substance:	**Tris(2,4-di-(tert)-butylphenyl)phosphite** CAS No. 31570-04-4 Batch No. N 26824 Purity > 99%
Method:	OECD 402, "Acute Dermal Toxicity," adopted February 24, 1987. 10 Rats (5 male and 5 female) were treated with a single dose (2000 mg/kg) of the test material applied to the skin (shaved area on the back of the animals representing about 10% of the body surface). The test material was evenly dispersed on the shaved skin and covered with a gauze lined semiocclusive dressing fastened around the trunk with an adhesive elastic bandage. After an exposure of 24 h, the skin was cleaned with lukewarm water and the dermal reaction was appraised. Animals were observed daily for clinical signs of toxicity and mortality for 14 days. Necropsy was performed at the end of the observation period.
Species/strain:	Rat [Tif:RAI f(SPF)]
No. Animals	10 (5 Male/5 Female)
Dose:	2000 mg/kg
Vehicle:	0.5% (w/v) carboxymethylcellulose in 0.1% aqueous polysorbate 80.
Exposure period:	24 h
Post-exposure observation:	14 days
GLP:	Yes
Year:	1992
Results:	LD_{50} > 2000 mg/kg body weight No mortalities occurred in this study. Piloerection and hunched posture were observed in some animals. These animals recovered within 2 days. No gross pathologic alterations were found at necropsy.
Remarks:	This study was assigned a reliability code of 1 (reliable without restrictions) according to the criteria established by Klimisch et *al* (1997).[2]
Reference:	'Acute dermal toxicity in the rat, Test No. 924065, TK 11582 (Irgafos 168), Ciba-Geigy Limited, Basel, Switzerland, 1992.

[2]See general reference, p. 53.

14. GENETIC TOXICITY IN VIVO

A. SISTER CHROMATID EXCHANGE

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4 Batch No. EN 008/77
Method:	Chinese hamsters were administered the test compound by gavage, and sacrificed 24 h after the exposure and 2 h after an i.p. injection of colcemide. Bone marrow was removed from the shafts of both femurs, and drop-preparations were made and stained according to a modified fluorochrome plus Giemsa technique.[4-6] Slides were scored for the number of sister chromatid exchanges.' 25 Differently stained metaphases of the second cell cycle with BUdR substitution were analyzed per animal. Initially slides from 2-3 animals/sex/dose and controls were examined. In the 1989 follow-up study, slides from up to 5 animals/sex/dose were evaluated.
Type:	Sister chromatid exchange
Species/strain:	Chinese hamster
Sex:	4-6 Males/4-6 Females per group
Route of Administration:	Gavage
Exposure period:	Single exposure
Doses:	1111, 2222, 4444 mg/kg (original study) 1777, 2666, 4000, 6000 mg/kg (follow-up study)
Vehicle:	Polyethylene glycol 400 (20 mL/kg)
Controls:	Concurrent Negative: Polyethylene glycol 400 (20 mL/kg) Positive: 7,12-Dimethylbenz(a)anthracene (DMBA) (100 mg/kg)
GLP:	No
Year:	1982, 1989
Results:	There was no evidence of significant treatment effect on sister chromatid exchange. This study was originally conducted in 1982 during which slides from 2 animals/sex/dose were analyzed. The numbers of SCE's in animals from and control and the 1111 and 2222 mg/kg groups were not significantly different. In the group treated with 4444 mg/kg, 1 of 4

animals showed an increased frequency of SCE's. To confirm these results, a second experiment with doses of 1777, 2666, 4000, and 6000 was performed. Based on data from 3 animals/sex/dose, the number of SCE's in all treatment groups showed no significant increase in comparison with the concurrent negative control. In 1989, slides from additional animals were analyzed, such that a total of 5 animals/sex/dose was examined. Based on this follow-up analysis, the number of sister chromatid exchanges per cell in animals treated with the 6000 mg/kg showed a small, but significant increase compared to control. The 6000 mg/kg dose exceeded the maximum recommended dose of 2000 to 5000 mg/kg, and this finding was interpreted as biologically not relevant.

Table 1. Initial results based on 2 animals/sex/dose

Group	Mean # SCE's per cell
Control (PEG 400)	4.21 ± 2.20
DMBA (100 mg/kg)	9.07 ± 3.93*
1111 mg/kg	4.69 ± 2.22
2222 mg/kg	4.62 ± 2.05
4444 mg/kg	6.26 ± 3.61*

*Statistically significant difference from control

Table 2. Initial results based on 3 animals/sex/dose

Group	Mean # SCE's per cell
Control (PEG 400)	4.39 ± 2.35
DMBA (100 mg/kg)	10.49 ± 6.09"
1777 mg/kg	4.63 ± 2.14
2666 mg/kg	4.57 ± 2.57
4000 mg/kg	4.85 ± 2.81
6000 mg/kg	4.90 ± 2.62

Table 3. Results based on 5 animals/sex/dose

Group	Mean # SCE's per cell
Control (PEG 400)	4.56 ± 2.32
DMBA (100 mg/kg)	11.93 ± 6.11
1777 mg/kg	4.76 ± 2.18
2666 mg/kg	4.64 ± 2.48
4000 mg/kg	4.94 ± 2.57
6000 mg/kg	5.17 ± 2.61*

*Statistically significant difference from control

Remarks: This study was not conducted under formal test guidelines. The study was assigned a reliability code of 2e, as it met generally accepted scientific standards, was well documented, and was acceptable for assessment.* The findings were consistent with another study of chromosomal aberrations, in which Chinese hamsters were administered the test compound (500, 1000, or 2000 mg/kg) daily for 2 days.[3] Analysis of cells from bone marrow did not reveal chromatid or chromosome-type aberrations.

References:

'"Sister chromatid exchange study, TK 11 682, Chinese hamster." Experiment No. 800586, Ciba-Geigy Limited, Basel, Switzerland, 1982.

[2]"Sister chromatid exchange study, Chinese hamster." Test No. 800586, Ciba-Geigy Limited, Basel, Switzerland, 1989.

[3]"Chromosome studies in somatic cells, TK 11 682, Chinese hamster." Experiment No. 783 106, Ciba-Geigy Limited, Basel, Switzerland, 1980.

[4]Perry, P. and Wolff, S., New Giemsa method of the differential staining of sister chromatids, Nature, 251, 156-158, 1974.

[5]Goto, K., Maeda, S., Kano, Y., and Sugiyama, T., Factors involved in differential Giemsa-staining of sister chromatids, Chromosoma, 66, 35 1-359, 1978.

[6]Allen, J.W., Shuler, C.F., Mendes, R.W., and Latt, S.A., A simplified technique for in vivo analysis of sister chromatid exchanges using 5-bromodeoxyuridine tablets, Cytogenet. Cell Genet., 18, 231-237, 1977.

'Perry, P. and Evans, H.J., Cytological detection of mutagen-carcinogen exposure by sister chromatid exchange, Nature, 258, 121-125, 1975.

[8]See general reference, p. 53.

B. CHROMOSOMAL ABERRATIONS

Test substance:	**Tris(2,4-di-(tert)-butylphenyl)phosphite** CAS No. 31570-04-4
Method:	The test compound was administered to male mice by gavage over a period of 10 days on days 0, 2, 3.5, and 9. Treatment groups consisted of 15 animals each and the control group consisted of 12 animals. Three days after the final dose and 3 h after an *i.p.* injection of colcemide, animals were killed, and drop-preparations were made of testicular parenchyma. Primary and secondary spermatocytes were assessed for chromosomal aberrations. Eight animals of the control group and 8 animals in each treatment group were examined. 100 Metaphases each of the primary and secondary spermatocytes were scored per animal. Among the spermatocyte I metaphases, the following aberrant forms were recorded: breaks; fragments; minutes; chromosome exchanges; atypical aberrations. Among the spermatocyte II metaphases: breaks; fragments; atypical aberrations.
Type:	Chromosome studies of spermatocytes
Species/strain:	Mouse (NMRI-derived strain)
Sex:	Male
Route of Administration:	Gavage
Exposure period:	Days **0, 2, 3, 5, 9**
Doses:	1481, 4444 **mg/kg** (in 20 **mL/kg** polyethylene glycol)
Control:	Concurrent, 20 **mL/kg** polyethylene glycol
GLP:	**No**
Year:	1982
Results:	No evidence of mutagenic activity of the test compound, as indicated by chromosomal aberrations. The chromosomal displays of the primary and secondary spermatocytes in the control group showed 5 aberrations out of 1600 metaphases, the 1481 **mg/kg** group showed 5 aberrations out of 1600 metaphases, and the 4444 **mg/kg** showed 2 aberrations out of 1600 metaphases.
Remarks:	This study was not conducted under formal test guidelines. The study was assigned a reliability code of **2e,** as it met generally accepted scientific standards, was well documented, and was acceptable for **assessment.**[2]

References: "'Chromosome studies in male germinal epithelium TK 11 682, mouse, test for mutagenic effects on spermatocytes." Experiment No. 782928, Ciba-Geigy Limited, Basel, Switzerland, 1982.

[2]See general reference, p. 53.

C. CHROMOSOMAL ABERRATIONS

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	The test compound was administered to male mice by gavage daily for 5 consecutive days (Days O-4). Treatment groups consisted of 15 animals and the control group of 12 animals. The animals were sacrificed on Day 5, 3 h after an *i.p* injection of colcemide (10 mg/kg). The testes of animals were processed, and drop-preparations were made of testicular parenchyma. 100 Spermatogonial metaphase plates from each of 8 animals in the control and treatment groups were examined for the following types of aberrations: chromatid aberrations; chromosomal aberrations; chromatid gaps; chromosomal pulverations.
Type:	Chromosome studies of spermatogonia
Species/strain:	Mouse (NMRI-derived strain)
Sex:	Male
Route of Administration:	Gavage
Exposure period:	5 Days
Doses:	1481, 4444 mg/kg (in 20 mL/kg polyethylene glycol 400)
Control:	Concurrent, 20 mL/kg polyethylene glycol 400
GLP:	No
Year:	1982
Results:	No evidence of mutagenic activity of the test compound, as indicated by chromosomal aberrations. The chromosomal displays from animals of the control and 4444 mg/kg groups showed no chromatid-type or chromosome-type aberrations. The 1481 mg/kg group showed 1 chromatid-type aberration in the form of a break. This incidence was within the frequency observed in historical controls, and can be considered spontaneous in origin.
Remarks:	This study was not conducted under formal test guidelines. The study was assigned a reliability code of 2e, as it met generally accepted scientific standards, was well documented, and was acceptable for assessment.[2]

References: "'Chromosome studies in male germinal epithelium, TK 11 682, mouse, test for mutagenic effects on spermatogonia." Experiment No. 782927, Ciba-Geigy Limited, Basel, Switzerland, 1982.

[2]See general reference, p. 53.

D. NUCLEUS ANOMALY

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	The test compound was administered by gavage daily for 2 consecutive days. Animals were sacrificed 24 h after the second administration, and bone marrow smears were made. Slides were stained in May-Grunwald solution and Giemsa. The slides of 3 animals/sex/group were examined, and 1000 bone marrow cells per animal were scored for the following anomalies: single Jolly bodies, fragments of nuclei in erythrocytes, micronuclei in erythroblasts, micronuclei in leucopoietic cells, and polyploid cells. In the positive control group, the slides of 4 female and 2 male animals were analyzed.
Type:	Nucleus anomaly test in somatic interphase nuclei
Species/strain:	Chinese hamster
Sex:	6 Males/6 Females/group
Route of Administration:	Gavage
Exposure period:	2 Days
Doses:	500, 1000, 2000 mg/kg/day
Vehicle:	Polyethylene glycol, PEG 400 (20 mL/kg)
Controls:	Concurrent Negative: PEG 400 (20 mL/kg) Positive: Cyclophosphamide (128 mg/kg)
GLP:	No
Year:	1980
Results:	The incidence of bone marrow cells with anomalies of nuclei was not significantly different between treatment and control groups.

Table 1. Percent of cells with anomalies of nuclei

Group	Animal No./Sex	Percent of cells with anomalies of nuclei*
Control (PEG 400)	1 F	0.1
	2F	0.1
	3F	0.2
	4M	0
	5 M	0.1
	6M	0.1
Cyclophosphamide (128 mg/kg)	1 F	6.5
	2F	6.3
	3 F	4.9
	4F	6.2
	5 M	14.7
	6M	8.8
500 mg/kg	1 F	0.2
	2F	0.3
	3F	0
	4M	0.1
	5 M	0
	6M	0.2
1000 mg/kg	1 F	0.3
	2F	0.1
	3F	0.2
	4M	0.1
	5 M	0.1
	5 M	0.1
2000 mg/kg	1 F	0.1
	2 F	
	3F	0.3
	4M	0.1
	5 M	0.1
	6M	0.1

*The total represents the sum of single Jolly bodies, fragments of nuclei in erythrocytes, micronuclei in erythroblasts, micronuclei in leucopoietic cells, and polyploid cells. The study reported separate incidences for each endpoint, butonlly the total is represented in this table.

Remarks: This study was not conducted under formal test guidelines. The study was assigned a reliability code of 2e, as it met generally accepted scientific standards, was well documented, and was acceptable for assessment.[2]

Reference:

"'Nucleus anomaly test in somatic interphase nuclei, TK 11 682, Chinese hamster." Experiment No. 78-3006, Ciba-Geigy Limited, Basel, Switzerland, 1980.

[2]See general reference, p. 53.

E. DOMINANT LETHAL

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Male mice (20/group) were administered a single dose of the test material by gavage. Each male was placed in a cage with 2 untreated females immediately after treatment. At the end of 1 week, the females were removed and replaced by another group of 2 females. The procedure was continued for 6 consecutive weeks. The females were examined daily for successful mating, as indicated by the occurrence of a vaginal plug. The day that the vaginal plug was observed was designated as Day 0 of gestation. Necropsy of the females were performed on Day 18 of pregnancy.
Type:	Dominant lethal
Species/strain:	Mouse, NMRI-derived (Tif:MAG f[SPF])
Sex:	Male, 20/group
Route of Administration:	Gavage
Exposure period:	Single exposure
Doses:	1000, 3000 mg/kg
Vehicle:	Aqueous carboxymethylcellulose
Control:	Concurrent, carboxymethylcellulose (0.2 mL/10 g body weight)
GLP:	No
Year:	1978
Results:	The females mated to treated males did not differ significantly from females mated to control, neither in mating ratio nor in the number of implantations and embryonic deaths (resorptions). There was no evidence of dominant lethal effects.

Table 1. Reproductive parameters

Dose group (mg/kg)	Mating Ratio	Number Pregnant	Mean Implantations	Live Embryos	Embryonic Deaths
Mating period 1					
0	31/40	27	9.37	90.1	9.9
1000	38/40	34	9.47	92.5	7.5
3000	34/40	29	10.17	89.5	10.5
Mating period 2					
0	34/40	27	10.67	89.6	10.4
1000	37/40	34	9.59	91.1	8.9
3000	31/40	28	9.61	88.5	11.5
Mating period 3					
0	35/40	32	10.72	88.6	11.4
1000	39/40	34	10.03	92.4	7.6
3000	32/40	28	9.57	92.5	7.5
Mating period 4					
0	33/40	27	10.37	95.4	4.6
1000	37/40	35	10.11	91.8	8.2
3000	31/40	29	10.14	89.5	10.5
Mating period 5					
0	31/40	28	10.29	91.7	8.3
1000	36/39	28	10.43	94.2	5.8
3000	32/40	28	10.89	93.4	6.6
Mating period 6					
0	31/40	26	10.85	91.5	8.5
1000	35/40	31	11.16	91.0	9.0
3000	31/40	23	10.96	91.7	8.3

Remarks: This study was not conducted under formal test guidelines. The study was assigned a reliability code of 2e, as it met generally accepted scientific standards, was well documented, and was acceptable for assessment.*

Reference: ""Dominant lethal study - TK11682 (Irgafos 168)." Project No. 784820, Ciba-Geigy Limited, Basel, Switzerland, 1978.

[2]See general reference, p. 53.

15. GENETIC TOXICITY IN VITRO

A. Mutagenic Effects in Bacteria

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	This study was not conducted under OECD guidelines, but was conducted using the methods described by Ames et *al.*[2-4] The material was tested for mutagenic effects on histidine auxotrophic mutants of *Salmonella typhimurium.* Cultures were prepared from frozen stock, and on the following day the standard plate test was carried out. The concentrations of the test substance were 0, 1, 3, 9, 27, 81 µg/0.1 mL. No rationale for dose selection was provided in the test report. Acetone was used for the negative control. In the experiments in which the substance was metabolically activated, 0.5 mL of the activation mixture (S9 fraction of liver from rats induced with Arochlor 1254 plus co-factors) was added. Positive controls were tested simultaneously, and included *N*-methyl-*N*'-nitro-*N*-nitrosoguaninde (TA 1535), 9(5)aminoacridine hydrochloride monohydrate (TA 1537), daunoblastin (TA (TA 100). The activation mixture was tested with TA 1535 and cyclophsophamide. In the experiments with and without the addition of microsomal activation mixture, 3 Petri dishes were prepared per strain and per group. In the positive control experiments, 2 Petri dishes were used per strain and per group. After incubation for 48 h at 37 °C, plates were analyzed for revertants.
Type:	Reverse mutation
System of testing:	*Salmonella typhimurium* TA 98, 100, 1535, 1537
Concentration:	0, 1, 3, 9, 27, 81 µg/0.1 mL
Metabolic activation:	With and without S9 liver fraction from rats induced with Arochlor 1254.
GLP:	No
Year:	1978
Results	The test material did not increase mutations with or without metabolic activation. Positive controls induced dose-related increases in the number of revertants.

Table 1. Mean revertants from experiments without metabolic activation

Dose	TA98	TA100	TA 1535	TA 1537
Control	13	78	8	6
1 µg/0.1mL	17	80	11	7
3	17	75	11	4
9	17	79	10	6
27	21	78	10	9
81	16	66	10	8

Table 2. Mean revertants from experiments with metabolic activation

Dose	TA98	TA100	TA 1535	TA 1537
Control	26	74	13	9
1 µg/0.1mL	17	84	14	10
3	32	84	14	8
9	26	87	12	9
27	29	92	12	9
81	28	84	13	10

Remarks: This study was not conducted under formal guidelines. However, the study met generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).[5]

References:

'"Salmonella/mammalian-microsome mutagenicity test with TK 11682." Experiment No. 78-2515, Ciba-Geigy Limited., Basel, Switzerland, 1978.

[2]Ames, B.N., Lee, F.D., and Durston, W.E., "An improved bacterial test system for the detection and classification of mutagens and carcinogens, Proc. Natl. Acad. Sci. USA, 70, 782-786, 1973.

[3]Ames, B.N., Durston, W.E., Yamasaki, E., and Lee, F.D., "Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection," Proc. Natl. Acad. Sci. USA, 70, 2281-2285, 1973.

[4]Ames, B.N., McCann, J., and Yamasaki, E., "Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test, Mutat. Res., 31, 347-364, 1975.

[5]See general reference, p. 53.

B. Mutagenic Effects in Yeast Cells

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4
Method:	Yeast cells in culture were centrifuged and resuspended in water to a density of 1 to 5 x 10^8 cells/r& The suspension (9 mL) was transferred to test bottles containing 1 mL of the test substance dissolved in DMSO. Following incubation for 3.5 h at 25 "C, the yeast cells were plated to determine the number of surviving cells and mutants.
System of testing:	*Saccharomyces cerevisiae* MP- 1
Concentration:	625, 1250, 2500, 5000, 10000 µg/mL
Metabolic activation:	No
GLP:	No
Year:	1982
Results	Not mutagenic

Table 1. Mutagenicity to *Saccharomyces cerevisiae* MP-1 *in vitro*

Test substance/ concentration	Surviving cells/ mL (x 10')	Intergenic recombination/ mL (x 10^4)	Intragenic recombination/ mL	Cycloheximide-resistant cells/ mL
DMSO	3.51	2.5	91	11
Irgafos 168				
625 µL/mL	4.02	1.5	123	9
1250 µL/mL	4.48	6.5	105	11
2500 µL/mL	3.97	2.5	110	8
5000 µL/mL	4.33	4.5	98	7
10000 µl/mL	2.37	0	67	4
4-Nitroquinoline-N-oxide				
1 µL/mL	2.55	183.0	2392	83
2 µL/mL	1.81	135.5	2158	53

Remarks: This study was not conducted under formal guidelines. However, the study met generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).[2]

Reference: "'Mutagenicity test on Saccharomyces cerevisiae MP-1 in vitro with TK 11 682." Experiment No. 820052, Ciba-Geigy Limited, Basel, Switzerland. 1982.

[2]See general reference, p. 53.

16. REPEATED DOSE TOXICITY

A. 2%Day Gavage Study in Rats

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	60 Rats (5 male and 5 female/group) were administered the test substance by gavage daily for 28 days. During the exposure period, animals were examined daily for clinical symptoms and body weight and weekly for food consumption. Ophthalmic examinations were performed pre-test and at week 4. Following final treatment, animals were sacrificed, and organs and tissues were examined macroscopically and microscopically. Additional rats (10 controls and 10 high dose group) were observed for 28 days post-exposure, and examined similarly at sacrifice.
Species/strain:	Sprague Dawley rat
No. animals/group:	5 Male and 5 Female/group
Route of administration:	Gavage
Exposure period:	28 Days
Frequency of treatment:	Daily
Post exposure observation period:	28 Days
Dose:	10, 50, or 250 mg/kg
Vehicle:	2% carboxymethyl cellulose
Control group:	Yes, concurrent vehicle
GLP:	No
Year:	1975
Results:	NOEL = 250 mg/kg/day No abnormal clinical symptoms were observed, and no animals died during the study. The test chemical did not significantly affect body weight or laboratory parameters (hematology and clinical chemistry). No effects of the test chemical were observed during necropsy or on histopathological examination.

Remarks: This study was not conducted under formal guidelines. However, the study met generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).[2]

Reference: '"28 Day oral toxicity study in rats with compound TK 11 682." Project No. 7DO3, Geigy Pharmaceuticals, Stamford Lodge, UK, 1975.

[2]See general reference, p. 53.

B. 90-Day Gavage Study in Rats

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4
Method:	220 Rats were assigned to one of five treatment groups, and were exposed to the test chemical by gavage daily for 13 weeks. During the exposure period, animals were examined daily for clinical symptoms and weekly for body weight and food consumption. For control and high-dose group animals, urinalysis was conducted during weeks 4, 12, and 17, hematology during weeks 0, 4, 12, and 17, blood chemistry during weeks 4, 12, and 17, and ophthalmic examinations during weeks 0, 6, 13, and 17. Following final treatment, animals were sacrificed, and organs and tissues were examined macroscopically and microscopically. Additional rats (10 controls and 10 high-dose group) were observed for 4 weeks post exposure, and examined similarly at sacrifice.
Species/strain:	Sprague Dawley rat
No. animals/group:	20 Male and 20 Female rats/dose group
Route of administration:	Gavage
Exposure period:	13 Weeks
Frequency of treatment:	Daily
Post exposure observation period:	4 Weeks
Dose:	125250,500, 1000 mg/kg/day
Control group:	Concurrent vehicle (1% caboxymethyl cellulose)
GLP:	No
Year:	1976
Results:	NOEL = 500 mg/kg/day No relevant clinical symptoms and no signs of systemic toxicity were observed during the study. The eye examinations and urine analysis revealed no deviations from controls. The body weight gain and the absolute and relative organ weights were within the control ranges, with the exception of higher kidney and thyroid weights among females at the end of the treatment. Higher kidney weights also were observed after the 4-week recovery period. The increased organ weights were not associated with histopathological changes, and were unlikely to be of toxicological significance.

Table 1. Summary data of mean organ weights, females, 13 weeks

Dose	Bodvweght, g	Kidney weight, g	Thyroid weight, mg
Control	325 ± 29.0	2.5 ± 0.2	19 ± 7.0
125 mg/kg/day	310 ± 28.5	2.5 ± 0.3	20 ± 5.2
250	316 + 24.3	2.5 + 0.2	24 + 6.4'
500	309 ± 27.9	2.7 ± 0.4'	27 ± 6.1'
1000	303 ± 18.0	2.7 ± 0.2*	25 ± 6.6'

*Statistically significant difference from control

Table 2. Summary data of mean organ weights, females, 13 weeks + 4 week recovery

Dose	Bodyweight, g	Kidney weight, g	Thyroid weight, g
Control	304 ± 26.1	2.5 ± 0.2	22 ± 4.0
1000 mg/kg/day	343 ± 42.4	3.1 ± 0.5*	23 ± 3.2

*Statistically significant difference from control

Remarks: This study was not conducted under formal test guidelines, but met generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).[2]

Reference: [1]"TK 11 682 Toxicity to rats, repeated oral administration for 13 weeks." Project No. CGB 167/76339, Huntingdon Research Centre, Huntingdon, UK, 1976.

[2]See general reference, p. 53.

C. 90-Day Feedii Study in Dogs

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	32 Dogs (16 male/16 female) were divided into one of four groups, and were fed the test compound (0, 719, 2208, or 8092 ppm) daily for 3 months. Additional animals (2 control and 2 high-dose group) were included to study recovery. Animals were examined daily for clinical symptoms, and food/water intake and weekly for body weight. Ophthalmic and hearing examinations were performed pretest and during weeks 4, 8, and 13 (and week 17 for recovery animals). Blood samples for hematology and clinical chemistry and urine samples were collected pretest and during weeks 4, 9, and 13 (and week 17 for recovery animals). During necropsy, organs and tissues were examined macroscopically and microscopically.
Species/strain:	Beagle dogs
No. animals/group:	4 Male and 4 Female/dose group
Route of administration:	Dietary
Exposure period:	3 Months
Frequency of treatment:	Daily
Post exposure observation period:	28 Days
Dose:	0, 1000, 3000, 10000 ppm (nominal) 0, 719, 2208, 8092 ppm (actual)
Control group:	Concurrent, control diet
GLP:	No
Year:	1978
Results:	NOEL > 3 18 mg/kg/day No abnormal clinical symptoms were observed, and no animals died during the study. Food and water consumption in all groups were similar. No effects were noted during eye and hearing tests. The test chemical did not significantly affect body weight or laboratory parameters (hematology, clinical chemistry, urinalysis). No effects of the test chemical were observed during necropsy or on histopathological examination. The NOEL was determined to be > 8092 ppm, which corresponds to 3 18 mg/kg/day.

Remarks: This study was not conducted under formal test guidelines, but met generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).[2]

Reference: [1]"3 Month dietary toxicity study in dogs with compound TK 11 682." Project No. 7DO3, Geigy Pharmaceuticals, Stamford Lodge, UK, 1978.

[2]See general reference, p. 53.

17. REPRODUCTIVE TOXICITY

Test substance:	**Tris(2,4-di-(tert)-butylphenyl)phosphite** CAS No. 31570-04-4 Batch No. EN 47503.22
Method:	Diets containing 0, 1600, 4000, or 10,000 ppm of the test material were fed continuously over the period of 18 weeks to parent F_0 and F_1. The periods of exposure included 12-day mating periods for each parental generation, starting 70 days after the initiation of dosing. The F_1 rats were additionally exposed to the test substance *in utero* and during lactation. Likewise, the F_2 generation was exposed to the test substance from embryogenesis through weaning. During the 12 day mating periods, females were mated overnight with males at a ratio of 1: 1. The day on which spermatozoa were found in the vaginal smear or a vaginal plug was found was designated as Day 0 of pregnancy. The females were then transferred to individual cages. Dams were allowed to rear their young to Day 23 postpartum The F_0 and F_1 parent rats were sacrificed after weaning of the F_1 and F_2 sucklings, respectively. Histopathological examination of organs was performed on all adults from the control and 10,000 ppm groups and a selected number of each of the F_1 and F_2 weanlings from these groups. For rats in the low and intermediate dose groups the tissues were retained for future reference.
Type:	Two-generation reproduction toxicity study
Species/strain:	Rat [Tif:RAI f(SPF)]
Sex:	Male/Female
Route of Administration:	Dietary
Exposure period:	18 weeks
Frequency of treatment:	Daily
Doses:	0, 1600, 4000, 10000 ppm
Control group:	Concurrent, standard diet
GLP:	Yes
Year:	1985
Results:	There were no effects of treatment on mating and pregnancy parameters, including mating rate, fertility index, implantation rate, litter size, male

to female sex ratio, and postpartum mortality) (Tables 1, 2). Transient reductions in body weight were observed among F_0 females exposed to 10,000 ppm and F_1 females exposed to 1600 ppm (Tables 3, 4). In animals from the other groups, including F_1 and F_2 weanlings, no differences in body weight were observed. The absolute and relative weights of several organs among F_0 and F_1 adults and F_1 and F_2 weanlings were affected by treatment (data presented in Tables 5-12). There were no clinical or systemic effects attributed to treatment, and there were no macro or histopathological findings that were related to the treatment.

Table 1. Reproductive parameters, F_0

	#Mated	#Pregnant	Implantation rate	Litter Size	% Male pups	%Loss (Day 21 postpartum)
Control	24/27	24	15.7 ± 2.3	14.3 ± 1.8	52.5	8.5
1600 ppm	25/28	24	16.7 ± 1.2	14.8 ± 1.8	51.7	3.1
4000 ppm	27/28	27	15.6 + 2.9	13.7 + 2.7	43.9	4.6
10000 ppm	23/28	19	14.6 ± 2.7	13.3 ± 2.6	44.7	4.7

Table 2. Reproductive parameters, F_1

	#Mated	#Pregnant	Implantation rate	Litter Size	% Male pups	%Loss (Day 21 postpartum)
Control	24/24	23	17.5 ± 3.5	13.9 ± 1.8	50.2	15.5
1600 ppm	20/24	20	15.5 ± 3.8	13.5 ± 3.6	54.5	13.2
4000 ppm	24/24	23	16.8 ± 2.1	14.7 ± 1.3	50.4	15.0
10000 ppm	22/24	21	17.0 ± 2.7	13.9 ± 2.2	49.1	11.7

Table 3. Maternal body weight during gestation, g

	Dose, ppm			
	0	1600	4000	10000
Day 0	289.5 ± 20.6	274.6 ± 21.8	275.2 ± 25.6	267.6 ± 27.1*
Day 6	313.1 ± 23.6	296.8 ± 22.8	296.4 ± 24.6	290.1
Day 11	333.3 ± 22.6	317.7 ± 23.3	316.7 ± 24.6	309.8
Day 16	366.3 ± 26.0	349.4 ± 26.6	347.6 ± 25.4	340.6 ± 32.0"
Day 21	431.1 ± 34.9	418.9 ± 31.8	416.9 ± 33.5	405.7 ± 41.5

*Statistically significant difference from control

Table 4. Maternal body weight during gestation, g

	Dose, ppm			
	0	1600	4000	10000
Day 0	281.1 ± 22.8	256.1 ± 21.4*	273.7 ± 33.3	273.6 ± 17.4
Day 6	301.8 ± 24.8	274.9 ± 20.5*	292.4 ± 31.8	293.4 ± 19.4
Day 11	322.6 ± 26.8	294.3 ± 20.4"	311.0 ± 31.2	311.3 ± 21.4
Day 16	354.9 ± 30.7	326.8 ± 23.4*	343.8 ± 29.6	342.4 ± 26.7
Day 21	423.4 ± 40.3	387.3 ± 35.3"	407.4 ± 32.7	402.7 ± 38.4

*Statistically significant difference from control

Table 5. Data for organs showing significant differences from controls: F_0 male adults, Week 18

Organ weights (g) and ratios	Dose, ppm			
	0	1600	4000	10000
Body	507.6	544.2	529.9	537.6
Brain	2.5	2.4	2.4	2.4
Brain/Body	0.488	0.449*	0.456*	0.452*
Liver	17.0	19.3*	18.2	18.7"
Liver/Body	3.355	3.545*	3.430	3.480"
Liver/Brain	693.8	796.8*	756.5"	775.3"
Spleen	0.74	0.73	0.67*	0.70
Spleen/Body	0.146	0.135	0.127*	0.131
Spleen/Brain	30.1	30.3	27.9*	29.2

*Statistically significant difference from control

Table 6. Data for organs showing significant differences from controls: F_0 female adults, Week 18

Organ weights (g) and ratios	Dose, ppm			
	0	1600	4000	10000
Body	302.9	297.9	294.0	291.0
Heart	1.16	1.12	1.11*	1.07*
Heart/Brain	51.1	49.7	49.9*	47.9*
Liver	12.7	12.5	12.3	10.9*
Liver/Body	4.19	4.21	4.20*	3.76*
Liver/Brain	558.7	556.7	554.0	489.2*

*Statistically significant difference from control

Table 7. Data for organs showing significant differences from controls: F_1 male weanlings, Week 17

Organ weights (g) and ratios	Dose, ppm 0	1600	4000	10000
Body	45.4	42.5	45.0	43.9

Table 8. Data for organs showing significant differences from controls: F_1 female weanlings, Week 17

Organ weights (g) and ratios	Dose, ppm 0	1600	4000	10000
Body	42.6	40.6	43.1	42.3
Spleen	0.21	0.18*	0.19	0.18
Spleen/Body	0.485	0.445	0.437*	0.422*

*Statistically significant difference from control

Table 9. Data for organs showing significant differences from controls: F_1 male adults, Week 35

Organ weights (g) and ratios	Dose, ppm 0	1600	4000	10000
Body	534.5	5 17.5	546.1	5 14.6

Table 10. Data for organs showing significant differences from controls: F_0 female adults, Week 35

Organ weights (g) and ratios	Dose, ppm 0	1600	4000	10000
Body	297.9	285.9	281.8*	296.7
Kidney	2.25	2.30	2.18	2.30
Kidney/Body	0.758	0.777*	0.776	0.786*
Spleen	0.56	0.52	0.52*	0.52
Spleen/Brain	24.5	22.8	23.4*	22.9

*Statistically significant difference from control

Table 11. Data for organs showing significant differences from controls: F_2 male weanlings, Week 34

Organ weights (g) and ratios	Dose, ppm 0	1600	4000	10000
Body	55.1	52.0	50.5	47.7
Brain	1.70	1.65	1.64	1.66
Brain/Body	3.16	3.29	3.35	3.53"
Liver	2.97	2.83	2.81	2.41*
Liver/Brain	174.4	170.4	170.5	145.4*

*Statistically significant difference from control

Table 12. Data for organs showing significant differences from controls: F_2 female weanlings, Week 34

Organ weights (g) and ratios	Dose, ppm 0	1600	4000	10000
Body	51.4	48.8	45.5	45.8
Heart	0.29	0.29	0.28	0.25*
Heart/Body	0.574	0.601	0.620*	0.55 1

*Statistically significant difference from control

Remarks: This study is assigned a reliability code of 1d (meets generally accepted scientific standards and is described in sufficient detail) according to the criteria established by Klimisch *et* al (1997).[2]

Reference: '"Report on Irgafos 168 (TK 11 682), Two-generation reproduction toxicity study in rats." Test No. 82 0873, Ciba-Geigy Ltd., 1985.

[2]See general reference, p. 53.

18. DEVELOPMENTAL TOXICITY/ TERATOGENICITY

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 3 1570-04-4 Batch No. EN 46776.12
Method:	OECD Guideline No. 414 (Teratogenicity). Females, 4-5 months old and weighing 3.0-3.2 kg, were mated by placing 1 female and 1 male per breeding cage. Each female was mated twice, the second time about 1 h after the first. This was designated was Day 0 of pregnancy. The test chemical was suspended in a 1: 1 mixture of PEG 400 and water, and administered by gavage to fertilized rabbits from day 6 until day 18 of pregnancy, inclusive. During the treatment period, the animals were checked daily for general body condition, weight gain, and symptoms. Food consumption was checked on days 6, 11, 15, 19, 24, and 29 of pregnancy. The dams were killed, and fetuses removed by Caesarean section on day 29 of pregnancy. During necropsy, dams and fetuses were examined per OECD guidelines.
Species/strain	Rabbit, chinchilla type
Sex:	20 females/dose group
Route of administration:	Gavage
Duration of the test:	29 Days
Exposure period:	Days 6 to 18 (inclusive)
Frequency of treatment:	Daily
Doses:	0, 200, 600, 1200 mg/kg body weight
Control group:	PEG 400/distilled water, 1: 1
GLP:	Yes
Year:	1983
Results:	This chemical was not embryotoxic, and did not produce teratogenic effects under the experimental conditions. There were no significant adverse effects on the dams and their progeny (no significant differences for litter parameters, values for pre-implantation loss, litter size and weight, skeletal anomalies and variants).

Table 1. Summary data of reproduction parameters

	Dose group (mg/kg/day)			
	0	200	600	1200
# Spontaneous deaths	0/20	2/20	2/20	4/20
# Females with corpora lutea	18/20	17/18	18/18	15/16
Corpora lutea/female	11.9 ± 3.5	11.8 ± 2.8	11.8 ± 2.6	11.9 ± 2.6
# Females with implantations	15/20	16/18	17/18	14/15
Implantations/female	9.9 ± 2.2	9.6 ± 2.7	9.3 ± 2.3	9.9 ± 2.3
# Females with abortions	0	0	0	0
Embryonal deaths (resorptions)	8.8	3.2	1.9	3.6
Fetal deaths (resorptions)	2.7	5.2	3.2	0.7
Dead fetuses	0	0	0.6	0
# Live fetuses (males/females)	72/59	74/67	74/75	63/69
Percent males	55.0	52.5	49.7	47.7
Mean weight of live male fetuses, g	35.5±8.1	36.7±8.9	40.2±8.1	37.9±7.3
Mean weight of live female fetuses, g	35.3±7.1	36.2±7.4	40.2±5.9	35.5±6.5

Remarks: This study is assigned a reliability code of 1 (reliable without restrictions) according to the criteria established by Klimisch et *al* (1997).[2]

Reference: '"Report on **Irgafos** 168 (TK 11 682) teratology study in rabbits." Test No. 82 0874, Ciba-Geigy Ltd., Basel, Switzerland, 1983.

[2]See general reference, p. 53.

GENERAL REFERENCE

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology. 25:* l-5, 1997.

Definition of codes

1 = Valid without restriction
la: GLP guideline study
lb: Comparable to guideline study
lc: Meets national standard methods (AFNOR/DIN)
1d: Meets generally accepted scientific standards and is described in sufficient detail

2 = Valid with restriction
2a: Guideline study without detailed documentation
2b: Guideline study with acceptable restrictions
2c: Comparable to guideline study with acceptable restrictions
2d: Meets national standard methods with acceptable restrictions
2e: Meets generally accepted scientific standards, well documented and acceptable for assessment
2f: Accepted calculation method
2g: Data from Handbook or collection of data

3 = Invalid
3a: Documentation insufficient for assessment
3b: Significant methodological deficiencies
3c: Unsuitable test system

4 = Not assignable
4a: Abstract
4b: Secondary literature
4c: Original reference not yet available
4d: Original reference in foreign language
4e: Documentation in sufficient for assessment